201-14155A

TEST PLAN FOR DIMETHYLOCTANAMIDE AND DIMETHYLDECANAMIDE (CHEMICAL ANALOGS)

OVERVIEW

The C.P. Hall Company agrees to sponsor N,N-dimethyloctanamide (CAS No. 1118-92-9) and N,N-dimethyldecanamide (CAS No. 14433-76-2) as two closely related analogs in the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. The company hereby submits a test plan and dossiers for these two substances. It is the intent of the sponsoring company to use existing data combined with structure activity relationships (SAR) to fulfill the Screening Information Set (SIDS) endpoints for environmental fate, ecotoxicity and human health effects.

Table 1. Test Plan Matrix for N,N-dimethyloctanamide (CAS No. 1118-92-9) and N,N-dimethyldecanamide (CAS No. 14433-76-2)

CAS Nos. 1118-92-9 and 14433-76-2	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
ENDPOINT	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYS/CHEM PROPERTIES							
Melting Point	Y(C8,C10)	N	Y	N	N	Y	N
Boiling Point	Y(M)	N	Y	N	N	Y	N
	E(B)	N	Y	Y	N	Y	N
Density	Y(C10)	Y	N	N	Y	Y	N
	Y(M)	N	Y	N	N	Y	N
Vapor Pressure	E(C8)	N	Y	Y	N	Y	N
	Y(C10)	Y	N	N	Y	Y	N
Partition Coefficient	Y(B)	Y	N	N	Y	Y	N
Water Solubility	Y(B)	Y	N	N	Y	Y	N
ENVIRONMENTAL FATE							
Photodegradation	Y(C10)	N	Y	N	Y	Y	N
Stability in Water	Y(C10)	N	Y	N	Y	Y	N
Biodegradation	Y(C10)	N	Y	N	Y	Y	N
Transport between Environmental Compartments (Fugacity)	E(B)	N	N	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y(M)	Y	N	N	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y(M)	N	Y	N	Y	Y	N
Toxicity to Aquatic Plants	Y(M)	Y	N	N	Y	Y	N
Toxicity to Terrestrial (NR)	Y(M)	N	Y	N	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y(M)	Y	N	N	Y	Y	N
Repeated Dose Toxicity	Y(M)	Y	N	N	Y	Y	N
Genetic Toxicity-Mutation	Y(M)	Y	N	N	Y	Y	N
Genetic Toxicity-Chromosomal Aberrations	Y(M)	Y	N	N	Y	Y	N
Toxicity to Reproduction	Y(M)[1]	Y	N	N	Y	Y	N
Developmental Toxicity	Y(M)	Y	N	N	Y	Y	N
OTHER TOXICITY DATA							
Skin Irritation (NR)	Y(M)	N	Y	N	Y/N	Y	N
Eye Irritation (NR)	Y(M)	N	Y	N	Y	Y	N
Sensitization (NR)	Y(M)	N	Y	N	Y	Y	N

Y = yes; N = no; E = estimated
(C8) = N,N-dimethyloctanamide only; (C10) = N,N-dimethyldecanamide only; (B) = both C8 and C10; (M) = mixture containing C8 and C10
[1] Reproductive organ toxicity data from 91-day study

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1. Introduction

The C.P. Hall Company submits this test plan for N,N-dimethyloctanamide (CAS No. 1118-92-9) and N,N-dimethyldecanamide (CAS No. 14433-76-2) for hazard review under the Environmental Protection Agency High Production Volume Chemical Program. The technical contact at this company is:

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2. Designation of Test Substance

Two chemical analogs are addressed in this test plan as follows:

$CH_3CH_2CH_2CH_2CH_2CH_2CH_2(C=O)N(CH_3)_2$

N,N-Dimethyloctanamide (CAS No. 1118-92-9)

and

$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2(C=O)N(CH_3)_2$

N,N-Dimethyldecanamide (CAS No. 14433-76-2)

These substances are chemical analogs with the same functionality, differing only in that N,N-dimethyldecanamide has two more carbons in its alkyl chain than N,N-dimethyloctanamide. N,N-dimethyldecanamide is available commercially as Hallcomid M-10®. N,N-dimethyloctanamide is not manufactured in pure form, but is commercially available as the major component in Hallcomid M-8-10®. Hallcomid M-8-10 contains (in weight %) 50-65% N,N-dimethyloctanamide and 37-50% N,N- dimethyldecanamide, with minor impurities N,N-dimethylhexanamide (0-5%) and N,N- dimethyldodecanamide (0-2%). This product will be referred to by its commercial name (Hallcomid M-8-10) for the remainder of this document. Both Hallcomid products are used principally as pesticide inert ingredients.

3. Criteria for Determining Adequacy of Data

All available studies were reviewed and assessed for adequacy according to the standards of Klimisch et al. (1997). Studies receiving a Klimisch rating of 1 or 2 were considered to be adequate.

4. Discussion of Available Test Information

The N,N- dimethyloctanamide and N,N- dimethyldecanamide test plan matrix (as shown in Table 1 on page 2) was constructed after a careful evaluation of all existing data (see below). This matrix is arranged by study type (columns) and screening data endpoints (rows), and indicates if data are provided for each end point in the sets of robust summaries. For the various endpoints data exist for one of the analogs, or for both analogs, or for the commercial product Hallcomid M-8-10. For endpoints where data are missing for one of the analogs, a structure activity relationship (SAR) approach is taken to use data for the other analog or for Hallcomid M-8-10 to predict behavior for the first analog.

4.1 Chemical and Physical Properties

The results of chemical/physical property testing are shown in Table 2.

Table 2. Chemical/physical properties of N,N-dimethyloctanamide and N,N-dimethyldecanamide

Endpoint	Value*	
	N,N-Dimethyloctanamide (CAS No. 1118-92-9)	N,N-Dimethyldecanamide (CAS No. 14433-76-2)
Molecular Weight grams/mol	171.28	199.34
Melting point (° C)	-27 to -22°C[a]	-11 to -7°C[a]
Boiling point (° C)	240 - 265.5 at 1015 hPa**,[b] *257.2 at 1016 hPa*	240 - 265.5 at 1015 hPa**,[b] *289.7 at 1016 hPa*
Relative Density	0.8835**,[b]	0.88 at 20°C[c]
Vapor pressure (hPa at 25° C)	*0 .026*	0.00114 [d] *0 .01*
Partition coefficient (Log Pow or Kow)	2.59 at 23° C[c] *2.46*	3.92 at 24°C[c] *3.44*
Water solubility (mg/l at 25 ° C)	4300 at 20°C[f] *372.3*	344 at 20°C[f] *19.8*

* Values shown in italics were estimated using the EPIWIN model program.
** Value is for Hallcomid M-8-10, a mixture containing 50-60% N,N-dimethyloctanamide and 35-45% N,N-dimethyldecanamide
[a]Internal communication from The C. P. Hall Company; [b] C. P. Hall Company MSDS ; [c]Krohn, 1995; [d]Krohn, 1994a; [e]Krohn, 1993; [f]Krohn, 1994b

4.1.1 Melting Point

Measured melting points were determined by the C. P. Hall Company using differential scanning calorimetry. The test materials were typical commercial Hallcomid M-10 (of =>98% purity) and Hallcomid M-8-10, which is a mixture containing 50-60% N,N-dimethyloctanamide and 35-45% N,N-dimethyldecanamide. Melting points were also estimated using EPIWIN MPBPWIN, but the values were much greater (40.1°C for N,N-Dimethyloctanamide and 60.8°C for N,N-

Dimethyldecanamide) than room temperature. Both products are known to be liquids at room temperature.

4.1.2 Boiling Point

A measured boiling point range of 240-265.5° C is available for Hallcomid M-8-10, a mixture containing 50-60% N,N-dimethyloctanamide and 35-45% N,N-dimethyldecanamide N,N-dimethyloctanamide (The C. P. Hall Company, 2002). Boiling points for the individual chemicals have been estimated by EPIWIN. These boiling points (257.2° C and 289.7° C for N,N-dimethyloctanamide and N,N-dimethyldecanamide, respectively) are in agreement with the measured boiling point for Hallcomid M-8-10, with an expected somewhat higher boiling point for N,N-dimethyldecanamide, which has a longer alkyl chain and higher molecular weight. These data are adequate for addressing this endpoint.

4.1.3 Vapor Pressure

The vapor pressure of 0.00114 hPa measured for N,N-dimethyldecanamide (Krohn, 1994a) is in close agreement with the EPIWIN estimate of 0.01 hPa. The EPIWIN estimate of 0.026 hPa for N,N-dimethyloctanamide is reasonable in comparison with the determinations for N,N-dimethyldecanamide, based on the expected somewhat higher volatility for the shorter chain, and lower molecular weight of N,N-dimethyloctanamide. These data are adequate for characterizing the vapor pressure for these substances

4.1.4 Octanol/Water Partition Coefficient

Log Pows of 2.59 and 3.92 have been determined for N,N-dimethyloctanamide and N,N-dimethyldecanamide (respectively), using ^{14}C-labeled test substance and following OECD Guideline No. 107 (Krohn, 1993). Values of ca. 2.46 and 3.44 (respectively) estimated by EPIWIN KOWWIN, are in the same ranges. These data are adequate for characterizing octanol/water partitioning for these substances.

4.1.5 Water Solubility

Water solubilities of 4.3 g/l and 344 mg/l have been determined for N,N-dimethyloctanamide and N,N-dimethyldecanamide (respectively), using ^{14}C-labeled test substance and following OECD Guideline No. 105 (Krohn, 1994b). EPIWIN WSKOW (v1.40) estimates somewhat lower respective values of 372.3 and 19.8 mg/l based on the estimated Log Kow values given above. It is likely that the measured values are more accurate than the estimated values. The data are adequate for characterizing water solubility of these substances.

4.1.6 Summary/Test Plan for Physical Properties

Both of the test substances are liquids with fairly high boiling points, low vapor pressures, limited water solubility, and positive partition coefficients. Measured data are available for both substances with respect to melting point, water solubility and partition coefficients. The measured density value for N,N-dimethyldecanamide is similar to the value measured for Hallcomid M-8-10, a mixture containing 50-60% N,N-dimethyloctanamide and 35-45% N,N-

dimethyldecanamide. EPIWIN appears to be a good model for estimating the vapor pressure for N,N-dimethyloctanamide, since the EPIWIN-estimated and measured values for dimethyldecanamide are in good agreement. Most measured values for the individual components and Hallcomid M-8-10 are similar to EPIWIN-estimated values, indicating that EPIWIN is a good model to predict physical properties of these materials, with the exception of melting points (see Section 4.1.1).

4.2 Environmental Fate/Pathways

Results of environmental fate modeling and studies are summarized in Table 3.

Table 3. Environmental fate parameters for N,N-dimethyloctanamide and N,N-dimethyldecanamide

Endpoint	**Value***	
	N,N-dimethyloctanamide (CAS No. 1118-92-9)	N,N-dimethyldecanamide (CAS No. 14433-76-2)
Photolysis (Atmospheric $T_{1/2}$, days) Direct Photolysis in air[a] Direct Photolysis in soil[b]	 No data No data	 >30 33
Indirect Photolysis (OH sensitizer) Hydroxyl Radical Rate Constant *cm^3/(molecule * sec)* Atmospheric $T_{1/2}$ (days)	 *2.7×10^{-11}* *0.4*	 *2.98×10^{-11}* *0 .4*
Stability in Water**	*Half-life >1 year*	*Half-life >1 year* Insignificant hydrolysis after 30 days at 25°C at pH 5,7,9[c]
Biodegradation	No data	50 % after 0.5 - 6.5 hrs[d,e] 90% after 0.65 - 7.5 days[d,e]
Henry's Law Constant (atm-m^3/mol)	*2.95×10^{-7}*	*5.2×10^{-7}*
Koc	*118*	*1,130*
Environmental transport (Fugacity Level III mass percentages)	*Air 1.6%* *Water39%;* *Soil 59.5%* *Sediment 0.23%*	*Air 1.19%* *Water 37.8%* *Soil 58.9%* *Sediment 2.09%*

*Values given in italics are estimated by EPIWIN.
**The test substances do not possess functional groups generally recognized to be readily hydrolyzable in water under neutral ambient conditions.
[a]Burri, 1995a; [b]Burri, 1996; [c]Burri, 1995b; [d] Flueckiger,1995; [e] Wyss-Benz and Tschech, 1995

4.2.1 Photodegradation

Direct photolysis of N,N-dimethyldecanamide has been determined in water (Burri, 1995a) and in soil (Burri, 1996), following EPA Guide-line subdivision N 161-2 and EPA Guide-line subdivision N 161-3, respectively. The results of these studies indicate that this substance is not

rapidly photolyzed in either medium. Atmospheric hydroxyl radical-induced photodegradation rate constants of ca. 2.7 x 10^{-11}cm^3/(molecule*sec) and 2.98 x 10^{-11}cm^3/(molecule*sec) have been estimated for N,N-dimethyloctanamide and N,N-dimethyldecanamide using EPIWIN AOP (v1.90). The same program estimates half-lives of 0.4 days for both substances for atmospheric photodegradation with hydroxyl radical as a sensitizer. These results are consistent for both analogs, and indicate that hydroxyl radical-induced atmospheric photodegradation proceeds readily, whereas direct photolysis in water or soil proceeds very slowly. No additional testing is necessary.

4.2.2 Stability in Water

The hydrolysis rate of N,N-dimethyldecanamide has been determined (Burri, 1995b) following EPA Pesticide Assessment Guidelines, Subdivision N. The results of this study indicate insignificant hydrolysis after 30 days at 25°C at pH 5, 7, and 9. EPIWIN modeling of both substances suggests that the amide group is the functionality in the molecule that is most susceptible to hydrolysis, and that hydrolysis at this position is extremely slow (half-life greater than one year). This result is consistent with the measured result and with generally recognized knowledge that amide functions are resistant to hydrolysis under neutral, ambient conditions. Because both test substances contain identical functional groups that are recognized to be resistant to hydrolysis, no testing of this endpoint is recommended.

4.2.3 Fugacity

Level III fugacity modeling has been conducted on the test materials using EPIWIN. The results are nearly identical for both chemical analogs, and indicate that the test substances will partition preferentially to water and soil. The model predicts that the lower homolog, N,N-dimethyloctanamide has a very slightly greater affinity for water. The calculated Henry's Law Constants of 2.95 x 10^{-7} and 5.2 x 10^{-7} atm-m^3/mol suggest that neither analog will rapidly volatilize from water, which in each case is the result of low vapor pressure. Volatilization from soil or sediment is also strictly limited. A soil adsorption/desorption study with N,N-dimethyldecanamide indicates that this material has low or low to medium mobility in soil (Morgenroth, 1995). Water soil partition constants (Koc) of 118 and 1,130 have been estimated using EPIWIN PCKOC for N,N-dimethyloctanamide and N,N-dimethyldecanamide, respectively. These values suggest (as would be expected) that the lower homolog would have somewhat higher soil mobility than N,N-dimethyldecanamide. Additional fugacity testing is not recommended.

4.2.4 Biodegradation

Two well-conducted studies performed with C^{14} labeled N,N-dimethyldecanamide indicate that this material rapidly biodegrades in soil (Flueckiger,1995; Wyss-Benz and Tschech, 1995). The rates of degradation of 50% and 90% of the material in different types of soil ranged from 0.5 to 6.5 hours, and 0.65 to 7.5 days, respectively. Since N,N-dimethyloctanamide is closely related in structure and chemical physical properties to N,N-dimethyldecanamide, this material is also expected to rapidly degrade in soil. Measured data are not available for biodegradation in water. The EPIWIN BIOWIN (v 4.00) program predicts that both substances are readily biodegradable. In addition, aliphatic amides are generally known to readily undergo biodegradation; first to

carboxylic acids, followed by further microcosm-induced breakdown. Results of the well-conducted biodegradation tests in soil, together with estimates from the EPIWIN/BIOWIN program are adequate to characterize this endpoint for N,N-dimethyloctanamide and N,N-dimethyldecanamide.

4.2.5 Summary/Test Plan for Environmental Fate Parameters

Level III fugacity modeling indicates that N,N-dimethyloctanamide and N,N-dimethyldecanamide will tend to partition to water and soil when released to the environment. Although both substances have low vapor pressures and moderately low Henry's Law Constants, EPIWIN modeling predicts that molecules entering the atmosphere will readily undergo hydroxyl radical-induced photodegradation. Well-conducted photodegradation studies are available for N,N-dimethyldecanamide in both soil and water. These studies indicate that the test substance is highly resistant to direct sunlight-induced photolysis in both media. The identical functionality of N,N-dimethyloctanamide suggests that this analog is also resistant to photolysis in these media. The abiotic hydrolysis of N,N-dimethyldecanamide has been studied at pH 3,5, and 7, indicating that this substance is resistant to hydrolysis at ambient temperatures, as is generally recognized for simple aliphatic amides. This study would predict similar behavior for the shorter chain analog, N,N-dimethyloctanamide .

Water-soil partition constants measured for dimethyldecanamide and estimated for N,N-dimethyloctanamide by EPIWIN predict some (albeit limited) soil mobility. Biodegradation studies and modeling indicate that N,N-dimethyldecanamide is readily degraded in soil and water. Modeling results, together with measured determinations of photolysis, hydrolysis and biodegradation are sufficient to characterize environmental fate end points for N,N-dimethyloctanamide and N,N-dimethyldecanamide at the screening level; therefore no further testing for these endpoints is planned.

4.3 Ecotoxicity

4.3.1 Acute Toxicity to Fish

A static, OECD guideline study in rainbow trout was performed with Hallcomid M-8-10 (Dogerloh, 1993). The no observable effect concentration (NOEC) and lethal concentration in 50% of the organisms (LC50) in this 96-hour study were 5 and 21.1 mg/l, respectively. None of the fish exposed to $\leq$ 15.8 mg/l died by 96 hours.

4.3.2 Acute Toxicity to Aquatic Invertebrates

A static EPA guideline study in Daphnia magna was performed with Hallcomid M-8-10 (Forbis, 1990). The NOEC and LC50 values in this 48-hour study were 4 and 7.7 mg/l, respectively.

4.3.3 Acute Toxicity to Aquatic Plants

The toxicity of Hallcomid M-8-10 to Selenastrum capricornutum was tested according to OECD Guideline 201 (Anderson, 1993). For inhibition of growth rate, the NOEC, and effective

concentration in 50% of the organisms (EC50) were 1.80 and 16.06 mg/l for 72 hours, respectively. For inhibition of biomass, the NOEC and the EC50 were < 1.80 and 5.47 mg/l, respectively. Although the pH of the control flasks was slightly higher (0.10 units) at the end of the study than the recommended value, this did not appear to adversely affect the outcome of the test.

4.3.4 Toxicity to other Non-Mammalian Terrestrial Species

Although not required, an EPA guideline test with Hallcomid M-8-10 was performed in bobwhite quail (Grau, 1994). Five groups of 10 birds (five per sex) were given a single oral dose of 0, 200, 400, 800 or 1600 mg/kg Hallcomid M-8-10 by gelatin capsule and observed for 14 days. None of the birds exposed to 800 mg/kg or less Hallcomid M-8-10 died. Transient signs of toxicity (ptosis, loss of equilibrium and/or apathy) were observed in 5 animals treated with 800 mg/kg. Five animals exposed to 1600 mg/kg died and all exhibited convulsions, ptosis, loss of equilibrium and/or apathy on the day of treatment. The no observable effect level (NOEL), lowest observable effect level (LOEL) and lethal dose in 50% of the animals (LD50) values were therefore 400, 800 and 1600 mg/kg, respectively.

4.3.5 Summary/Test Plan for Ecotoxicity

Results of guideline studies in rainbow trout, Daphnia magna and Selenastrum capricornutum show that Hallcomid M-8-10 is of moderate toxicity to these species. An additional study indicates that Hallcomid M-8-10 is of low toxicity to bobwhite quail. The studies that have been performed adequately assess the toxicity of Hallcomid M-8-10 to fish, aquatic invertebrates, algae and birds. Since this material predominantly contains N,N- dimethyl octaneacidamide and N,N- dimethyl decaneacidamide (in approximately equal amounts), and the two materials are closely related in chemical structure and physical properties, the potential for ecotoxicity of the two chemical analogs is not expected to differ substantially from that of Hallcomid M-8-10. Therefore, additional testing with the individual analogs is not necessary.

4.4 Human Health Data

4.4.1 Acute Mammalian Toxicity

This endpoint is filled by sufficient oral, inhalation and dermal toxicity studies in rats performed with Hallcomid M-8-10 (Kreuzmann, 1990a, Pauluhn, 1991, Bomann, 1995). The LD_{50} and LD_{100} (lethal dose in 10%% of animals) values for the oral study were 1,250 mg/kg and 2,500 mg/kg, respectively. The NOEC and LC50 value for inhalation were 118.5 mg/m^3 and greater than 3551 mg/m^3, respectively. The dermal LD_{50} values were 2000 mg/kg for males and between 400 and 2000 mg/kg for females. The NOEL for systemic effects in the dermal study was 200 mg/kg.

Symptoms observed in rats orally treated with 1,250 to 5,000 mg/kg Hallcomid M-8-10 included ataxia, depression, and labored breathing prior to death. Piloerection, red stains around nostrils, brownish urine stains and/or hunched posture were noted up to study day 4 in surviving rats treated with 1.25 or 2.5 g/kg (3/4 and 1/4, respectively). Rats treated orally with 0.025 g/kg

exhibited signs of toxicity only on the day of dosing. Survivors appeared normal after approximately day 5, and had normal necropsies at study termination.

In rats exposed to 586.4 mg/m^3 Hallcomid M-8-10 for 4 hours by inhalation, signs of toxicity such as reddening of the nose, reduced motility and piloerection occurred on the day of exposure only. Most of the rats exposed to higher concentrations also exhibited additional signs and symptoms of respiratory irritation. Symptoms in rats exposed to 2007.6 or 3550.7 mg/m^3 persisted for up to 7 and 14 days, respectively. The necropsy of the one animal that died after exposure to 3550.7 mg/m^3 revealed distended, liver-like and edematous lungs, hydrothorax, and reddened and swollen rhinarium. Surviving rats exposed to 3550.7 mg/m^3 also had a higher incidence of distended lung. Animals exposed to lower concentrations did not exhibit any gross pathological changes with respect to controls.

In the dermal study, four out of 5 females exposed to 400 mg/kg and all rats exposed to higher concentrations exhibited clinical signs of toxicity. These signs generally occurred within 30 minutes of treatment and reversed within 6 days treatment. Skin irritation was noted at the site of administration of most animals exposed to 200 mg/kg, all animals exposed to 400 mg/kg, and all males exposed to 2000 mg/kg. The skin effects lasted from day 2 until the end of the study. One female treated with 50 mg/kg had some squamation at the treatment area. Since none of the others treated with 50 mg/kg had skin reactions, this dose was chosen as the threshold level for local effects.

Since Hallcomid M-8-10 predominantly contains N,N-dimethyloctanamide and N,N-dimethyl decanamide (in approximately equal amounts), and the two materials are closely related in chemical structure and physical properties, the potential for acute mammalian toxicity of the two chemical analogs is not expected to differ substantially from that of Hallcomid M-8-10. Therefore, additional acute toxicity testing with the individual materials is not necessary.

4.4.2 Repeated Dose Mammalian Toxicity

Four repeated dose toxicity studies have been performed with Hallcomid M-8-10. The critical study for the endpoint was a 91-day oral dietary study performed according to OECD guideline 408 (Wirnitzer and Ruhl-Fehlert, 1993). The no observable adverse effect level (NOAEL) for Hallcomid M-8-10 in this study was 2,000 ppm (136.8 mg/kg/day for males and 178.5 mg/kg/day for females), and the lowest observable adverse effect level (LOAEL) was 10,000 ppm (787.6 mg/kg/day for males and 894.6 mg/kg/day for females). Effects noted at 10,000 ppm included emaciation (5/10 males), decreased body weight gain (which normalized during a 28 day recovery period), increased serum cholesterol, increased liver weight, and pathological changes in the kidneys (males only). Similar findings were observed in rats ingesting 10,000 ppm Hallcomid M-8-10 in a 28-day range finding study (Wirnitzer, 1993).

In dogs treated orally by gavage with 20, 100, or 500/1000 mg/kg Hallcomid-M-10 for 6 weeks, no effects were noted at 20 mg/kg/day (Vliegen, 1996). The study personnel set the NOAEL at 100 mg/kg/day; however, the data suggested that there were some treatment-related effects at this dose (i.e. increased vomiting, salivation, and liver, kidney and pancreas weights). Dogs dosed with 500 mg/kg/day for two weeks and 1000 mg/kg/day for the remainder of the study

exhibited vomiting, salivation, increases in some liver enzymes, and increased liver, kidney and pancreas weights.

A five day inhalation study of Hallcomid M-8-10 in rats was conducted according to OECD guidelines (Pauluhn, 1992). In this study, rats were exposed (head and nose only) to an aerosol containing 24.6, 111.2 and 521.2 mg/m^3 material with an average MMAD (and GSD) of 1.4 (1.5) microns. The NOAEL and LOAEL in this study were 111.2 and 521.2 mg/m^3, respectively. Effects noted at 521.2 mg/m^3 included difficulties in breathing, reduced motility, hypothermia and weight loss during treatment, and pathological changes in the nasal and paranasal cavities (females only) after a 15-day recovery period. Lesions in other organs were not observed at necropsy.

Since Hallcomid M-8-10 predominantly contains N,N-dimethyloctanamide and N,N-dimethyl decanamide (in approximately equal amounts), and the two materials are closely related in chemical structure and physical properties, the potential for repeated dose mammalian toxicity of the two analogs is not expected to differ substantially from that of Hallcomid M-8-10. Therefore, additional repeat dose toxicity testing with the individual materials is not necessary.

4.4.3 Genetic Toxicity

4.4.3.1 Mutagenicity

Hallcomid M-8-10 tested negative for mutagenicity in an Ames test (OECD 471) involving *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 in the absence and presence of a metabolic activation system (Herbold, 1992) and a HGPRT assay (OECD 476) conducted with V79 Chinese hamster lung cells in the absence and presence of a metabolic activation system (Brendler-Schwaab, 1994).

The potential for mutagenicity of N,N-dimethyloctanamide and N,N-dimethyldecanamide is not expected to differ substantially from that of Hallcomid M-8-10, since they are the predominant ingredients. Therefore, mutagenicity testing with the individual materials is not necessary.

4.4.3.2 Chromosomal aberration

An OECD Guideline 473 study has been conducted with Hallcomid M-8-10 in Chinese Hamster Ovary Cells in the absence and presence of a metabolic activation system (Gahlmann, 1995). In this study, incubation with up to 160 micrograms/ml (without activation) and 180 micrograms/ml (with activation) did not lead to an increase in the number of aberrants with respect to historical controls. The finding of an increased number of aberrants at 8 hours for cells treated with 180 micrograms/ml in the presence of a metabolic activation system with respect to the solvent control was considered by study personnel to be due to the unusually low number of solvent control cells with aberrations (0.5%).

Based on the fact that N,N-dimethyloctanamide and N,N-dimethyldecanamide are the predominant ingredients of Hallcomid M-8-10 and have similar structures and physical properties, the results of the study with Hallcomid M-8-10 are likely to be predictive of those

with the individual chemical substance analogs. Therefore, additional chromosomal aberration testing with the individual analogs is not necessary.

4.4.3.3 Additional Studies

The ability of Hallcomid M-8-10 to cause unscheduled DNA synthesis in rat primary hepatocytes in the absence of metabolic activation was tested according to OECD Guideline 402 (Brendler-Schwab, 1994). At concentrations up to 98.8 micrograms/ml (the highest concentration that did not cause excessive toxicity), there was no increase in nuclear labeling or the percentage of cells in repair.

4.4.4 Reproductive Toxicity

No mating studies with the individual chemical analogs or Hallcomid M-8-10 have been performed. However, the 91-day rat dietary study that was conducted with Hallcomid M-8-10 included examination of reproductive organs (Wirnitzer and Ruhl-Fehlert, 1993). In this study, the NOAEL for reproductive effects was 10000 ppm, which was higher than the NOAEL for systemic effects. Changes in the testes, prostate and/or epididymis that were noted in 1-2 males from the control, low and high dose groups were not considered to be related to treatment since the incidences and degrees of severity of the lesions in were low (with the exception of one low dose animal that had a high degree of tubular atrophy in the testes) and not dose-dependent.

Results of the developmental toxicity studies (see Section 4.4.5 below) indicate that treatment with up to 450 mg/kg/day Hallcomid M-8-10 in rats or 1000 mg/kg/day of Hallcomid M-8-10 in rabbits during organogenesis has no effect on the number of resorptions, implantations, corpora lutea or viable or nonviable fetuses. At the clearly maternally toxic dose of 450 mg/kg/day, rats had a small increase in post-implantation (embryonic) loss (9.4% vs. 5.6% in controls).

Altogether, the results of the repeated dose and developmental studies suggest that the potential for reproductive toxicity of Hallcomid M-8-10 is low. Therefore, reproductive toxicity testing with N,N-dimethyloctanamide and N,N-dimethyldecanamide is not necessary.

4.4.5 Developmental Toxicity

Results of two OECD guideline studies show that Hallcomid M-8-10 is not a developmental toxicant at non-maternally toxic doses. In a study in rats treated with 50, 150 or 450 mg/kg/day Hallcomid M-8-10 from Days 5 though 15 of gestation (Becker and Biedermann, 1991a), 50 mg/kg/day was the NOAEL for maternal toxicity. Reduced food consumption was observed in dams treated with 150 mg/kg/day (the LOAEL), and more severe signs of toxicity (ventral recumbancy, dyspnea, apathy, coma, and weight loss) were noted in dams treated with 450 mg/kg. Treatment with 50 or 150 mg/kg/day had no effect on any reproductive or fetal parameter. Treatment with 450 mg/kg/day was associated with increased post-implantation (embryonic) loss, reduced fetal weight, and an increased incidence of fetuses (and litters) with skeletal abnormalities (eg. wavy ribs and dumbbell-shaped thoracic bodies) and variations (e.g. non-ossified or incompletely ossified vertebrae, sternebrae or metatarsala). Study personnel did not consider the abnormal skeletal findings in fetuses from dams treated with the high dose to be

indicative of a specific teratogenic effect of the test article because they are commonly found in Wistar rats and correlated with reduced fetal weight.

The results of the OECD study in rabbits (Becker and Biedermann, 1991b) show that Hallcomid M-8-10 is not a developmental toxicant at doses up to 1000 mg/kg/day, which was a maternally toxic dose. Although a number of skeletal variations were observed in this study, there appeared to be no clear-cut, dose-dependent differences in the incidences of variants between treated and control animals. Therefore, study personnel did not consider them to be related to administration of test material.

As the results of the developmental studies with Hallcomid M-8-10 are likely to be predictive of results for N,N-dimethyloctanamide and N,N-dimethyldecanamide, no additional testing is necessary.

4.4.6 Additional Data

4.4.6.1 Skin and Eye Irritation

The results of a DOT corrosivity potential study performed in 6 rabbits indicate that Hallcomid M-8-10 causes moderate-severe skin irritation but is not corrosive (Harris, 1990). An additional skin irritation study performed in one rabbit indicates that the material is corrosive (Kreuzmann, 1990b). Altogether, these results suggest that Hallcomid M-8-10 is severely irritating to the skin. Due to the suspected irritation potential of Hallcomid M-8-10, the material was tested for eye irritation in a single young adult male New Zealand White rabbit (Kreuzmann, 1990c). The total irritation scores ranged from 26 (at 1 hr) to 66 (at Day 4), indicating that the material was highly irritating.

Based on the fact that the two chemical analogs are the predominant ingredients of Hallcomid M-8-10 and have similar structures and physical properties, the results of the study with Hallcomid M-8-10 are likely to be predictive of those with the individual analogs. No additional testing is necessary.

4.4.6.2 Sensitization

The ability of Hallcomid M-8-10 to produce sensitization has been tested in a GLP study in guinea pigs (Kreuzmann, 1990c). After initiation with the highest dose that did not cause irritation (5% test material in 80% ethanol/20% distilled water), challenge with 2.5% test material in acetone did not produce skin irritation. Therefore, Hallcomid M-8-10 did not cause sensitization in the guinea pig. Based on the rational presented above, the results of this study are likely to be predictive of results with N,N-dimethyloctanamide and N,N-dimethyldecanamide. Therefore, testing of these chemical analogs is not necessary.

4.4.7 Summary/Test plan for mammalian toxicity

Adequate studies with Hallcomid M-8-10 have been conducted for all required endpoints. Acute oral, inhalation and dermal toxicity studies show that exposure to fairly large amounts of Hallcomid M-8-10 is required to produce acute toxicity. Inhalation of a very high concentration

(521 mg/m^3) for 5 days causes toxicity to the respiratory system of rats (but not other organs). Results of an OECD guideline, 91-day oral study show that repeated ingestion of doses up to approximately 800 mg/kg/day for 91 days is well tolerated in rats. The material is irritating to the skin and eyes, and is not a sensitizer. Repeated exposure to doses equal to or greater than 100 mg/kg/day also appears to be irritating to the GI tract of dogs, as evidenced by vomiting and increased salivation after dosing. Adequate studies show that Hallcomid M-8-10 is not mutagenic or clastogenic. Results of the 91-day test indicate that the material is not toxic to reproductive organs, and developmental studies in rats and rabbits indicate that the material is not a developmental or reproductive toxicant.

Since Hallcomid M-8-10 predominantly contains N,N-dimethyloctanamide and N,N-dimethyl decanamide (in approximately equal amounts), and the two materials are closely related in chemical structure and physical properties, the potential for mammalian toxicity of the two chemical analogs is not expected to differ substantially from that of Hallcomid M-8-10. Therefore, additional mammalian toxicity testing with the individual materials is not necessary.

5. Summary

In summary, valid data are present to satisfy all physical/chemistry, environmental, aquatic and mammalian toxicity endpoints. In general, measured physical chemistry values for N,N-dimethyloctanamide, N,N-dimethyldecaneacidamide and Hallcomid M-8-10 are similar to each other and to EPIWIN-estimated values for the individual components, indicating that EPIWIN is a good model to predict physical properties and environmental fate of these materials, that data for one analog will be predictive of the other, and those data for Hallcomid M-8-10 can be used to predict behavior of the individual components. No additional testing is necessary.

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